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BOVINE ABORTION ASSOCIATED WITH RENAL OXALOSIS IN THE FETUS

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Introduction

THE CAUSE OF BOVINE ABORTION is established in only 15–20% of cases (35). A recent survey conducted in the northeastern region of the United States incriminated an infectious agent in 23.3% of 3812 aborted bovine feti (14). Another survey in the Northern Plains States of the U.S. determined the cause in 35.3% of 2544 abortion cases (25). This latter survey included dystocias and anomalies.

Noninfectious agents such as chemicals, drugs and poisonous plants are known abortifacients; hormonal, physical and nutritional factors as well as genetic or chromosomal abnormalities have been reported to cause abortion (35). Little information is available regarding frequency of occurrence of such instances. Recently, Beck (4) has drawn attention to the fact that many potentially dangerous substances, such as analgesic agents, antimicrobials, antihistamines, tranquilizers, sedatives, cardiovascular drugs, and other drugs, can cross the placental barrier. It is therefore reasonable to assume that consideration must be given to a much wider range of agents which might affect the fetus.

This study was prompted by the observation of structures resembling oxalate crystals in the kidneys of aborted bovine feti[1,2] and of oxalate crystals in an alleged case of acorn poisoning in a day old calf.[3] Objectives of the work reported here were: to determine whether the crystals observed were, in fact, oxalate, and to gather information about the incidence of such deposits in fetal tissues.

Materials and Methods

All bovine feti or fetal tissues submitted to the Provincial Veterinary Laboratory, Regina, Saskatchewan and the Department of Veterinary Pathology, Western College of Veterinary Medicine, Saskatoon, Saskatchewan from July 1, 1971 to June 30, 1973 were included in this study. A total of 1509 cases were examined. For comparison, kidneys from 121 randomly sampled calves aged one to 30 days were studied during March, April, and May, 1973. These animals had died from various causes, the most common of which was neonatal diarrhea. Ten cases of oxalate nephrosis in dogs and cats were also examined using the same histochemical procedures as those conducted on the fetal and neonatal tissues.

Necropsy examination

Feti were examined by routine necropsy and tissues were collected for cultural and microscopic procedures. If the entire fetus was available, the abomasum was ligated at the ruminal-omasal junction and pylorus for submission to the diagnostic bacteriological laboratory. Portions of lung, liver, spleen and kidney were collected as aseptically as possible for virological studies. Similar tissues were fixed in 10% neutral buffered formalin for histological examination.

Microbiological examination

Routine bacteriological procedures for isolation of such known pathogens as *Brucella* spp., *Vibrio* spp. and mycotic agents were conducted on all samples.

Commencing in January, 1972, fluorescent antibody procedures were performed on frozen sections of tissue for the detection of infectious bovine rhinotracheitis (IBR) and bovine viral diarrhea (BVD) antigens. Bovine kidney cell

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[1]Chalmers, G. A., Lethbridge, Alta. and R. G. Christian, Edmonton, Alta., Personal Communication, 1973.

[2]R. E. Moffatt; Personal observation, Necropsy case N72-599, February 16, 1972, Dept. Vet. Pathology, Saskatoon, Sask.

[3]Olander, H. J. Case No. 34. 23rd Annual Seminar, A.C.V.P., Atlanta, Ga., November 1972.

cultures were inoculated with tissue extracts and observed for the presence of cytopathic effect. Identification procedures were carried out on any agents found. Diagnosis of epizootic bovine abortion (EBA) was made on the basis of gross and histological lesions compatible with those described in the literature (22). The diagnosis of parainfluenza-3-virus (PI_3) infection was also made on the basis of histological lesions (42).

Histological examination

Formalin-fixed tissues were routinely processed, embedded in paraffin, sectioned at 6μ and stained with hematoxylin-eosin (H & E). When indicated by this examination the following special stains were used:

Gomori's Methenamine Silver Nitrate technique (Grocott stain) and the Periodic Acid-Schiff reaction for the demonstration of mycotic agents (31).

Brown and Brenn's Gram stain for identification of bacteria (31).

H & E stained sections were examined under both normal and polarized light. When crystals suggestive of calcium oxalate were found, tissues were subjected to the following procedures:

von Kossa reaction for the demonstration of calcium (31).

Alizarin-Red-S method for demonstration of calcium (30).

Pizzolato's (33) Peroxide Silver method for calcium oxalate.

Roscher's Ca-naphthalhydroxamate method for oxalates (36).

2M acetic acid test (20); acetic acid does not dissolve oxalate crystals.

Concentrated sulfuric acid test (11); oxalates are dissolved by sulfuric acid.

Results

Abortion Cases

Results of the two-year survey are given in Tables I, II and III. Presence of focal hepatic necrosis (e.g. in many cases of IBR abortion) and congenital anomalies were the primary gross lesions detectable. Following are the anomalies observed, with numbers of cases in brackets: Arthrogryposis (21); cardiac anomaly (10); cleft palate (9); Hydrocephalus (6); transposition of aorta (5); monster (3); congenital pulmonary cysts (2); osteopetrosis (2); intestinal segmental aplasia (2); ectopia cordis (2); chondrodysplasia (1). In the other cases, however, no specific changes could be seen. Serosanguinous fluid in body cavities, perirenal hemorrhage and advanced autolysis were common to all forms of abortion.

Infectious agents known to cause abortion were identified in 491 out of 1509 cases (32.5%). The largest single cause (15.4% of the total) was IBR virus infection. Presently recognized non-infectious conditions were thought to be the principal reason for abortion in an additional 118 cases (7.8%), thus increasing the percentage of definitive diagnoses to 40.3%.

In 545 accessions where kidneys were available for study, crystals (Figure 1) were found in 257 (47.2%). Crystals observed were light yellowish brown and often present in rosette formation with radial symmetry (Figure 2). The number and shape was not readily determined when examined with ordinary light; under polarized light, this was very easily appreciated. The degree of crystal deposition varied considerably. Figures 3 and 4 are representative of a case with rather extensive crystal deposits. Birefringent crystals were found in renal tubules and in the pelvis but not in other organs examined. Advanced cytoplasmic and nuclear degenerative changes in tubular epithelium of some feti were taken as an indication of nephrosis provided that all other renal structures such as glomeruli and vascular elements were well preserved. No attempt was made to assess the incidence of nephrosis as many kidneys had evidence of advanced autolysis.

In most instances, the von Kossa stain failed to demonstrate the crystals observed under polarized light; in addition, the anisotropism of the crystals was lost with this procedure. Pizzolato's method stained crystals brown to black, affording easy recognition (Figure 3). The Ca-naphthalhydroxamate method demonstrated the crystals quite well especially when examined under polarized light (Figure 4). Alizarin-Red-S failed to demonstrate the crystals consistently although in some instances the periphery of the crystals was faintly positive (Figure 5).

In a small number of instances, mineralization of renal tissue and/or hepatic tissue could be seen in H & E-stained tissue sections under normal illumination. Such deposits stained faintly with the Pizzolato stain, taking a golden brown tint which was distinctly different from those stained black. These mineral deposits were anisotropic as well; however, no radial or rosette formation was found. Crystals which were positive for oxalate on the special stains did not dissolve with 2M acetic acid but could be removed easily by concentrated sulfuric acid.

Newborn Calves

Crystals resembling those observed in renal tissue of aborted feti were found in 27 out of 121 (22.3%) kidneys of newborn calves. Such deposits were seen primarily in younger ani-

TABLE I

INFECTIOUS CAUSES (BACTERIAL) OF ABORTION IN SASKATCHEWAN 1971–1973

	Regina		Saskatoon		
Diagnosis/Year	1971–72	1972–73	1971–72	1972–73	Total
Brucellosis					
no kidney[a]	0	4	2	1	7
oxalate +[b]	0	0	0	0	0
oxalate −[c]	0	0	1	1	2
Vibriosis					
no kidney	13	5	0	0	18
oxalate +	1	5	1	1	8
oxalate −	0	1	2	0	3
C. pyogenes					
no kidney	16	12	4	6	38
oxalate +	0	3	0	5	8
oxalate −	0	2	1	4	7
E. coli					
no kidney	4	8	3	1	16
oxalate +	0	2	0	2	4
oxalate −	0	2	3	0	5
Streptococcus spp.					
no kidney	3	3	1	1	8
oxalate +	0	2	0	2	4
oxalate −	1	0	2	1	4
Pasteurella spp.					
no kidney	7	5	0	0	12
oxalate +	1	3	0	0	4
oxalate −	0	0	0	0	0
Leptospirosis					
no kidney	1	0	0	0	1
oxalate +	0	0	0	0	0
oxalate −	0	0	0	0	0
Other					
no kidney	2	4	0	3	9
oxalate +	0	1	0	0	1
oxalate −	0	0	1	1	2

[a]no kidney = kidney not available for histological study
[b]oxalate + = oxalate crystals found
[c]oxalate − = no oxalate found

mals; in only two cases were crystals found in calves older than two and one-half weeks.

Carnivores

Kidneys of carnivores in which a diagnosis of oxalate toxicosis had been made were subjected to the same histological procedures as described previously. Crystals compatible with oxalate were readily demonstrated by the Pizzolato stain and the Ca-naphthalhydroxamate stain. It was found that a large number of crystals also reacted positively when von Kossa or Alizarin methods were employed.

DISCUSSION

Nature of the crystals

In the past, identification of calcium oxalate in tissue has been based on x-ray diffraction or chemical analysis. As pointed out by Johnson and Pani (20), neither procedure is convenient for *in situ* investigations. Successful attempts have been made to develop new reliable histochemical reactions, i.e. the Pizzolato stain (33) and the Roscher technique (36). Of the stains employed in this study, the von Kossa procedure was unsuitable. This stain demonstrates calcium phosphate rather than calcium oxalate (2). The Alizarin-Red-S stain, under conditions of the histochemical procedure used, appears to react primarily with the carbonates of calcium, strontium and barium rather than the oxalate salts of these minerals as suggested by Johnson and Pani (20).

Pizzolato's (33) and Roscher's (36) methods were found to be very satisfactory. Our results suggest that the crystals present in fetal and post-natal kidneys examined were, in fact, oxalates. Different staining characteristics of those crystals present in the carnivore kidney would

TABLE II

INFECTIOUS CAUSES (VIRAL, MYCOTIC, PROTOZOAL) OF ABORTION IN SASKATCHEWAN 1971–1973

	Regina		Saskatoon		
Diagnosis/Year	1971–72	1972–73	1971–72	1972–73	Total
Viral					
IBR					
no kidney[a]	81	40	23	16	160
oxalate +[b]	2	8	3	1	14
oxalate −[c]	2	16	15	26	59
EBA					
no kidney	0	8	2	1	11
oxalate +	0	8	0	0	8
oxalate −	0	0	0	0	0
PI_3					
no kidney	0	4	0	1	5
oxalate +	0	4	0	0	4
oxalate −	0	2	2	2	6
BVD					
no kidney	0	0	0	0	0
oxalate +	0	0	0	0	0
oxalate −	0	0	0	1	1
Cytomegalo-virus					
no kidney	0	0	0	0	0
oxalate +	0	0	0	0	0
oxalate −	0	0	0	1	1
Mycotic[d]					
no kidney	7	19	4	4	34
oxalate +	0	6	1	0	7
oxalate −	1	11	2	5	19
Protozoal					
Toxoplasmosis					
no kidney	0	0	1	0	1
oxalate +	0	0	0	0	0
oxalate −	0	0	0	0	0

[a]no kidney = kidney not available for histological study
[b]oxalate + = oxalate crystals found
[c]oxalate − = no oxalate found
[d]*Aspergillus* spp., phycomycetes and yeasts.

suggest that mineral deposits other than oxalate were involved in these cases as well.

Significance of oxalate crystals in renal tissue

Although traditional thinking has held that renal damage in cases of oxalate toxicosis is due to the obstructive effects of the calcium oxalate crystals, recent studies (19, 36) suggest that the oxalate ion rather than the calcium oxalate crystal is responsible for the renal damage. Oxalic acid causes intracellular demineralization and cell death resulting in nephrotoxicity (4). In addition, oxalate competitively inhibits enzymatic oxidation of lactate, interferes noncompetitively with reduction of pyruvate, and inhibits dehydrogenase (16). Demonstration of oxalate crystals in the kidney and associated damage therefore is an indication of existing toxicosis.

Oxalate poisoning in Ruminants

Oxalate poisoning in sheep is well documented (2, 7, 10, 17, 18, 19, 32, 39, 44, 45, 46). Although cattle have been reported resistant to oxalate poisoning (21), this is not substantiated by other reports (6, 8, 9, 15, 27, 28, 29, 38, 45). In addition, there is one report of renal oxalosis in a deer (48). Among the signs and gross pathological findings described are gastritis, diarrhea in nursing calves, renal oxalosis, locomotor disturbances, hyperexcitability and tetany. To our knowledge, there are no reports associating fetal death with oxalate poisoning.

Source of Oxalate

Endogenous sources – Hyperoxaluria may result from several mechanisms which have not all as yet been confirmed. Primary hyperoxaluria induced by hereditary defect occurs in man (13). Vitamin B_1, B_6 and folic acid are important participants in the metabolism of amino acids such as glycine and serine. If the pathway of glyoxylic acid to formic acid and CO_2 is blocked, it is suggested that the urinary excretion of oxalate may increase (43). Calcium oxa-

TABLE III

NONINFECTIOUS CAUSES OF ABORTION IN SASKATCHEWAN 1971–73

Diagnosis/Year	Regina		Saskatoon		Total
	1971–72	1972–73	1971–72	1972–73	
Nutritional					
Iodine deficiency					
no kidney[a]	3	2	0	0	5
oxalate +[b]	0	0	0	0	0
oxalate −[c]	0	0	1	1	2
Vit. A deficiency					
no kidney	0	1	0	0	1
oxalate +	0	0	0	0	0
oxalate −	0	0	0	0	0
Twinning[d]					
no kidney	7	7	2	1	17
oxalate +	0	2	0	0	2
oxalate −	0	4	0	0	4
Anomaly					
no kidney	1	10	8	17	36
oxalate +	1	11	1	5	18
oxalate −	0	5	0	4	9
Dystocia (Stillbirth)					
no kidney	2	9	1	1	13
oxalate +	0	0	0	0	0
oxalate −	0	6	1	4	11
Undetermined					
no kidney	281	195	38	58	572
oxalate +	5	96	16	58	175
oxalate −	8	83	19	43	153

[a]no kidney = kidney not available for histological study
[b]oxalate + = oxalate crystals found
[c]oxalate − = no oxalate found
[d]Suggested cause of abortion due to competition for nutrients (35).

TABLE IV

COMPARISON OF INCIDENCE OF RENAL OXALOSIS IN IBR, ANOMALIES, UNDETERMINED CAUSES OF ABORTION AND IN POSTNATAL CALVES

	Number of cases with kidneys available for study	Oxalate +	%
IBR	73	14	19.2
Anomaly	27	18	66.7
Undetermined cause of abortion	328	175	53.3
Postnatal calves	121	27	22.3

late crystals may be found in small numbers in patients with uremia but also occur with diseases of the liver, pancreas, intestine and in conditions of shock (lower nephron nephrosis) (1, 40). Whether any of the possibilities mentioned above occurs in the bovine species is unknown at present.

Exogenous Sources – The result of ingestion of ethylene glycol is well documented in man, carnivores (for review see Kersting and Nielsen 23, 24) and poultry (34). High levels of oxalate may be found in plants such as sugarbeets (*Beta saccharifera*), rhubarb (*Rheum rhaponticum*), halogeton (*Halogeton glomeratus*), greasewood (*Sarcobatus vermiculatus*), pigweed (*Amaranthus reflexus*), soursob (*Oxalis cernua*), sorrell (*Rumex acetosa*), and a variety of grasses (16), all of which are palatable to livestock. In addition, many species of fungi prevalent in temperate climates are capable of degrading basic food substrates to oxalate. Examples of these are *Aspergillus niger* and *Aspergillus flavus* (12, 16, 26, 47). In all these circumstances of exogenous poisoning one has

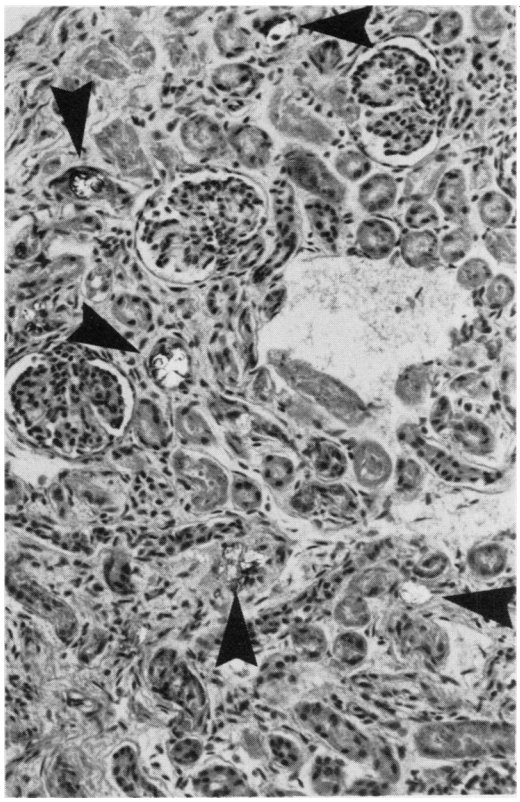

FIGURE 1. Oxalate crystals (*arrows*) in renal tubules of a bovine fetus. Polarization filters partially crossed. H & E stain. ×160.

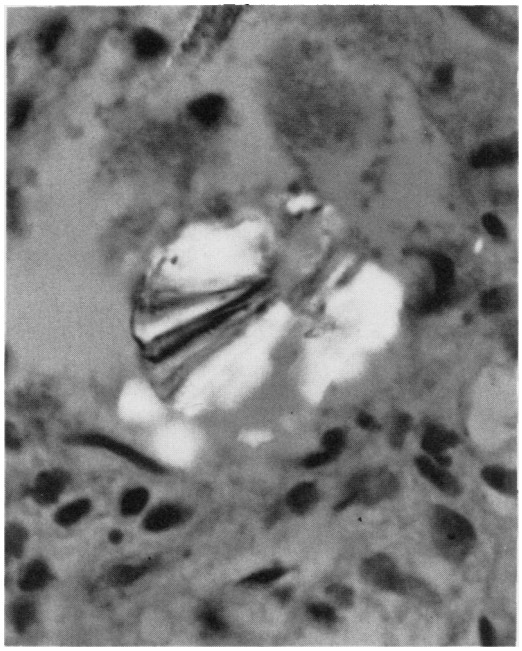

FIGURE 2. Oxalate crystal, displaying rosette formation. Polarized light. H & E stain. ×1000.

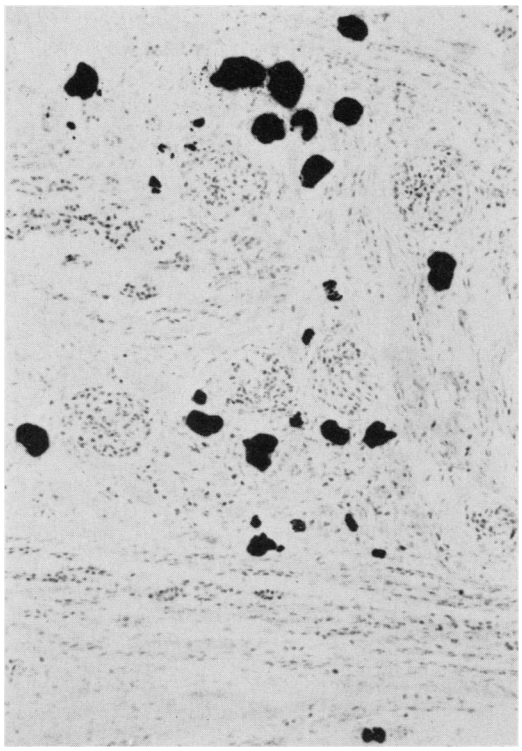

FIGURE 3. Demonstration of oxalate (black) by Pizzolato's method in a fetal kidney. Pizzolato stain. ×100.

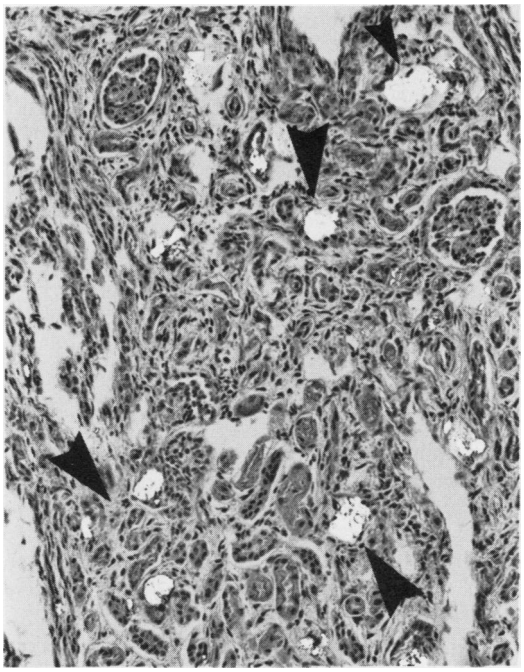

FIGURE 4. Demonstration of Calcium-naphthalhydroxamate crystals (*arrows*) by Roscher's method. Polarization filters partially crossed. Roscher stain. × 100.

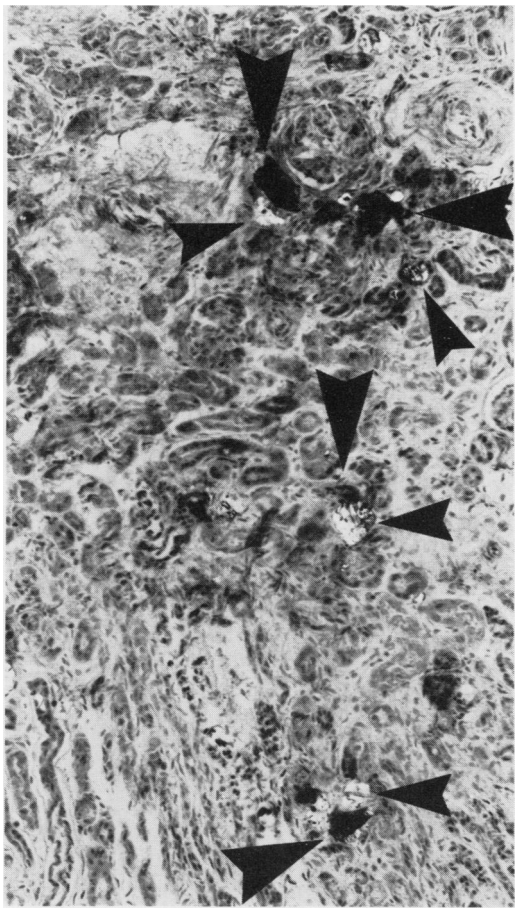

FIGURE 5. Oxalate crystals (*large arrows*), which are birefringent under examination with polarized light, and deposits of calcium (*small arrows*) in the periphery of the oxalate crystals. Alizarin-Red-S method. ×100.

to speculate that some of the oxalic acid, taken up by the dam, crosses the placenta and eventually is excreted through the fetal kidney.

If one assumes that mouldy foodstuff could be the principal source of oxalate, a hypothesis which has yet to be proven,[4] one must bear in mind that mouldy foodstuff might be contaminated with mycotoxins, such as Ochratoxin A. This mycotoxin has been shown to cause fetal death (41). In a recent study, Ochratoxin A was found in 18 out of 29 samples of heated grain from Saskatchewan farms (37). Whether a relationship exists between fetal oxalosis and death due to Ochratoxin has not been investigated.

Significance of fetal and postnatal renal oxalosis

Oxalate crystals were found in 175 cases (53.3%) in which no other etiological diagnosis could be made, and in 66.7% of the cases with anomalies. In contrast to this, only 19.2% of the IBR-abortion group and 22.3% of postnatal calves were positive for oxalate (Table IV).

In comparing the results of the Regina laboratory with those of the Saskatoon laboratory, it was evident that the incidence of oxalate crystals in the Regina accessions was slightly higher (161 cases out of 305, i.e. 52.7% positive) than in the Saskatoon accessions (96 cases out of 240, i.e. 40.0% positive). At present, it is not known whether this is a reflection of possible regional differences in sources of oxalates, or a reflection of different feeding practices.

Crystals were found also in feti in which other infectious agents were identified. These findings suggest that oxalate may predispose the fetus to secondary infection, abortion or stillbirth. It is interesting to note that the 19.2% of the IBR-group represent approximately the same percentage as found in postnatal calves (22.3%). One might speculate that in about 20% of pregnancies, oxalate crystals are present in kidneys without causing fetal death, unless complicated by viral or other infection, but predisposing the calf to postnatal disease.

It should be emphasized that this study does not prove beyond doubt that oxalosis may cause fetal death. It is merely intended to report these findings. A detailed discussion of the pathogenesis, possible relationship between oxalosis and anomaly, predisposition to other infectious diseases, and the prevention of the condition is beyond the scope of this work. Further studies on the effect of oxalate on ruminal gastrointestinal function and effects on the fetus are indicated.

SUMMARY

From a total of 1509 bovine abortions in Saskatchewan (July 1, 1971 – June 30, 1973), kidneys of 545 cases were examined for presence of oxalate crystals. Oxalates were found in 175 out of 328 cases (53.3%) in which an etiological cause could not be established, and in 18 out of 27 cases (66.7%) with congenital malformations. In contrast to this, only 14 out of 73 cases (19.2%) of IBR abortions had renal oxalosis. A comparative study of postnatal calves up to 30 days of age revealed presence of oxalate crystals in 27 out of 121 cases (22.3%). Although the source was not established, it was considered

[4]In the spring of 1973, a limited number of questionnaires were sent to farmers in Saskatchewan on whose premises bovine renal oxalosis had been diagnosed. Although some of those returned indicated that pigweed and greasewood were present in the area, a larger number pointed out that mouldy feed and hay or slough hay had been fed for some time prior to the abortions.

that the oxalates might originate from mouldy feed.

Résumé

Les auteurs ont procédé à la recherche de cristaux d'oxalate dans les reins de 545 des 1509 avortons bovins qu'ils ont examinés en Saskatchewan, du 1er juillet 1971 au 30 juin 1973. Ils en décelèrent dans 175 (53.3%) de 328 cas d'avortement d'étiologie indéterminée, ainsi que chez 18 (66.7%) de 27 avortons atteints d'anomalies congénitales. Par ailleurs, seulement 14 (19.2%) sur un total de 73 cas d'avortement attribuables à la rhino-trachéite infectieuse manifestaient de l'oxalose rénale. Une étude comparative portant sur 121 veaux âgés d'un à 30 jours révéla la présence de cristaux d'oxalate dans les reins de 27 d'entre eux (22.3%). Bien qu'ils n'aient pu en déterminer la source, les auteurs pensent que ces oxalates proviendraient d'aliments moisis.

Acknowledgments

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ADDENDUM

Can. vet. J. 15: 39–41. 1974

Since this paper was published the authors located an early Canadian report of canine coccidioidomycosis which was not included in recent reviews.

PLUMMER, P. J. G. Coccidioidomycosis with a pathological report of a case in a dog. Can. J. comp. Med. 5: 146–148. 1941.